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MERCHANT & GOULD PC P.O. BOX 2903 MINNEAPOLIS, MN 55402-0903			EXAMINER JOHANNSEN, DIANA B	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/581,611	Applicant(s) BERNS ET AL.	
	Examiner Diana B. Johannsen	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 November 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-40 is/are pending in the application.
- 4a) Of the above claim(s) 19-36,38 and 40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37 and 39 is/are rejected.
- 7) ☒ Claim(s) 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 June 2006 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>0607</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This application is a 371 of PCT/IB04/04405, filed December 3, 2004. The international search report and written opinion for the PCT application have been received and considered.

Election/Restrictions

2. Applicant's election with traverse of Group II (claims 37-40), and of the species of the combination of gene markers SIAH-2 and DEME-2, in the reply filed on November 30, 2009 is acknowledged. The traversal is on the ground(s) that "it would not be unduly burdensome for the Examiner to search and examine" all the claims and all the species. This is not found persuasive because it does not address the basis of the restriction and species election in the present case. Search burden is not an applicable criterion when restricting a 371 application; rather, the claims were restricted into 2 Groups, and a species election applied, because unity of invention was found to be lacking for the reasons stated in the Election/Restriction mailed September 30, 2009. Applicant has not addressed the issue of unity, and the claims have not been amended, such that the same requirement applies to the claims now pending. Accordingly, applicant's arguments are not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 19-36, 38 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention (claims 19-36) and non-elected species (claims 38 and 40, which each require analysis of either an 81 gene or 44 gene

panel), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 30, 2009.

Priority

4. It is noted that provisional application 60/527,608 does not disclose a relationship between the elected marker combination of SIAH-2 and DEME-6 and outcome of anti-estrogen therapy. Accordingly, the earliest application in which the elected invention was disclosed is PCT/IB04/04405, filed December 3, 2004.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Drawings

6. The drawings are objected to because the text of Figure 2 is too small to be clearly legible upon printing. **Applicant's attention is also drawn to the fact that the descriptions of Figures 2 and 4 reference color Figures, while the figures provided are in black and white. If color figures were in fact provided in the 371 application (such that they may be filed in the present application without introducing new matter), applicant may wish to file those color Figures (along**

with the appropriate petition and fee) in the instant application, particularly in view of the rejections below that relate to applicant's reliance on expression patterns depicted in Figure 2A.

7. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., pages 12-13). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See

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MPEP § 608.01. It is noted that this objection may be overcome by simply deactivating the embedded hyperlinks by deleting the recitation <http://>.

Claim Objections

9. Claim 39 is objected to because of the following informalities: item(c) of the claim references “positive Progression Free Survival” rather than “positive prediction of Progression Free Survival”. (Please note the prior reference in item(c) to a “negative prediction of Progression Free Survival”.) Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 37 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37 and 39 are indefinite over the recitation of the limitation “two or more marker genes identified in Table 1 as differentially expressed in primary tumors of recurring breast cancer patients exhibiting an outcome to anti-estrogen therapy with a significance of $p \leq 0.05$ ” in each of the claims. It is noted that applicant has elected the combination of markers SIAH-2 and DEME-6 for examination. It is unclear how the reference in the claims to Table 1 or particular characteristics of the Table are further limiting with respect to the elected invention. Further, Table 1 of the specification does not include any recitation of a group of markers, such that it appears the claims may have been intended to reference a different Table or Figure. Additionally, to the extent

that the claims incorporate information from Table 1 or any other Table/Figure, the language of the claim does not make clear what elements of the Table/Figure are required and which are not. Accordingly, the reference in the claims to “Table 1” renders the claims indefinite.

Claims 37 and 39 are indefinite over the recitations in the claims of “Cluster 1” and “Cluster 2” expression patterns. Page 4 of the specification teaches that “Cluster I and Cluster II gene profiles are shown in Figure 2A as correlating with progressive disease (Cluster I) and objective response (Cluster II)”. However, while the description of Figure 2A specifies that upregulated genes are shown in red and downregulated genes in green, the figures provided in the application are not in color. Accordingly, it is not possible to inspect Figure 2A and make a determination as to what expression patterns characterize each Cluster, and thus it is unclear what patterns are encompassed by the terms “Cluster 1” and “Cluster 2”. Please see also the rejection under 35 USC 112, first paragraph below, and the objection to the drawings noted above. It is again noted that applicant may be able to file color drawings without introducing new matter if such drawings were in fact present in the PCT application of which the instant application is a 371.

Claims 37 and 39 are indefinite because it is unclear how the “correlating” of (c) actually relates to the prior method steps or to the “predicting” of the preamble of the claims. The “correlating” step appears to constitute a recitation of characteristics of Cluster 1 and 2 expression patterns; there is no apparent nexus between this “correlating” and the generating of a prediction of outcome based on the prior steps of

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“analyzing” and “determining”. Accordingly, the language of the claims should be clarified to make clear how (c) relates to the rest of the claim and results in “predicting” outcome/Progression Free Survival.

Claim Rejections - 35 USC § 112, first paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)). It is noted that the examiner has considered all of the evidence related to each of these factors, and that

those factors, reasons and evidence that have led to a conclusion that enablement is lacking are discussed below (*MPEP* 2164.04).

Claims 37 and 39 each require steps of “a) analyzing a patient’s primary tumor for expression of two or more marker genes” and “b) determining if the expression pattern of said tumor-s marker genes correlates with a Cluster 1 or Cluster 2 expression pattern.” Claim 37 is drawn to a method “for predicting outcome of anti-estrogen therapy for recurrent breast cancer” including a final step (c) of “correlating a Cluster 1 expression pattern with prediction of Progressive Disease and Cluster 2 expression pattern with Objective Response to anti-estrogen therapy for recurrent breast cancer”. Claim 39 is drawn to a method “for predicting Progression Free Survival of anti-estrogen therapy for recurrent breast cancer” including a final step (c) of “correlating a Cluster 1 expression pattern with a negative prediction of Progression Free Survival for recurrent breast cancer and a Cluster 2 expression pattern with a positive Progression Free Survival for recurrent breast cancer.” The terms “Objective Response” and “Progressive Disease” are defined at page 4 of the specification. It is again noted that applicant has elected the combination of gene markers SIAH-2 and DEME-6.

It is unpredictable as to whether one of skill in the relevant art could actually use applicant’s claimed invention. As noted above, steps b) and c) of the claims require the correlating of expression patterns with Cluster 1 and 2 expression patterns. Page 4 of the specification teaches that “Cluster I and Cluster II gene profiles are shown in Figure 2A as correlating with progressive disease (Cluster I) and objective response (Cluster II)”. However, while the description of Figure 2A specifies that upregulated genes are

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shown in red and downregulated genes in green, the figures provided in the application are not in color. Accordingly, it is not possible to inspect Figure 2A and make a determination as to what expression patterns characterize each Cluster, and thus it is unclear what patterns are encompassed by the terms "Cluster 1" and "Cluster 2".

Because the claims as written require the use of Cluster 1 and Cluster 2 as depicted in Figure 2A, and one of skill in the art could not in fact employ Figure 2A as required to practice the claimed invention, the specification does not enable the practice of the claimed invention. Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for further guidance with regard to the enablement of a claimed invention. However, in the instant case, no teachings of the prior art are informative with regard to what might be encompassed by "Cluster 1" and "Cluster 2" of the instant claims. With regard to the elected SIAH-2 and DEME-6 markers, it is noted that the prior art as exemplified by Nakamura et al (US 7,531,300 B2 [May 2009; filed Sept 2004]) does teach differential expression of both SIAH-2 and DEME-6 in ER-positive as compared to ER-negative tumors (see entire reference, particularly col 38, lines 1-21, Fig 3, and Table 2), and further that the prior art as exemplified by Ayers et al (US 7,504,222 B2 [March 2009; filed Oct 2002]) teaches both overexpression of DEME-6 in ER-positive tumors (see entire reference, particularly col 12, lines 9-16, Table 2) and the known association between ER-positive tumors and tamoxifen susceptibility (col 91, lines 19-33). Thus, the teachings of the prior art do support applicant's evidence and data as presented in Example 5 and Tables 3-6 regarding the use of SIAH-2 and DEME-6 as markers in predicting tamoxifen response. However, the

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claims as written require comparisons/correlations with the specific expression patterns of "Cluster 1" and "Cluster 2" of Figure 2A. (Further, it is also noted that absent the availability of Figure 2A in a form that can be accurately interpreted, it is not possible to determine whether the noted prior art references teach or suggest the particular correlations required by the claims.) As these expression patterns are not available for use, even an infinite quantity of experimentation would be insufficient to practice the claimed invention. As such a type and quantity experimentation is clearly undue, it would require, it would require undue experimentation to use applicant's claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634